Dual-Phase ^{99m}Tc-Sestamibi Imaging: Its Utility in Parathyroid Hyperplasia and Use of Immediate/Delayed Image Ratios to Improve Diagnosis of Hyperparathyroidism

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Objective: Dual-phase ^{99m}Tc-sestamibi (methoxyisobutylisonitrile [MIBI]) imaging is the technique of choice for hyperparathyroidism (HPT), especially for localizing parathyroid adenomas. Prior studies have shown its utility for detecting hyperplasia is equivocal, but we believe this is not true. We attempted to quantitate the region-of-interest counts per pixel between immediate images and delayed images (I/D ratio) and use this ratio to distinguish normal parathyroid versus hyperplasia versus adenoma.
Method: Anterior pinhole and upper thorax images with a low-energy, high-resolution collimator at 20 min and 2 h after ^{99m}Tc-MIBI injection were obtained on 54 subjects. The results were analyzed retrospectively as hyperplasia, adenoma, or normal parathyroid by the persistence of activity in 2 or more foci, a solitary focus, or no activity on the delayed images. These interpretations were compared with pathology when available. I/D ratios were computed for all scans, and mean ratios were calculated for each type of pathology (normal parathyroid, hyperplasia, and adenoma). The resulting ratios were analyzed with a *t* test to determine significant differences between the ratios.
Results: Sensitivity and specificity were 96% and 88%, respectively, for parathyroid hyperplasia. Mean I/D ratios were 2.26 ± 0.68, 2.80 ± 0.95, and 3.10 ± 0.77 for subjects with hyperplasia, adenoma, and normal parathyroid, respectively (hyperplasia vs. normal, $P = 0.020$; adenoma vs. normal, $P = 0.381$; hyperplasia vs. adenoma, $P = 0.033$).
Conclusion: Dual-phase ^{99m}Tc-MIBI imaging is more sensitive and specific for parathyroid hyperplasia than reported previously, supporting its use to localize hyperplastic glands preoperatively and to help guide resection. A thyroid ratio between immediate and delayed images will aid in distinguishing hyperplasia from normal parathyroid in uncertain cases.

Key Words: hyperparathyroidism; ^{99m}Tc-sestamibi; dual-phase parathyroid imaging

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Primary hyperparathyroidism (HPT) has an incidence of 100–200 per 100,000 in the general population. The etiology is unknown, but data from parathyroid adenomas and hyperplasia support a genetic cause linked to chromosome 11, which is also implicated as the cause of type I multiple endocrine neoplasia. Ninety-five percent of cases of primary HPT are caused by adenomas (80%–85%) or hyperplasia (10%–15%) (*1*). Adenomas are nearly always solitary. Hyperplasia usually involves all 4 glands but can involve only 2 or 3 glands and occur with varying degrees of asymmetric glandular involvement. Secondary HPT is another cause of parathyroid hyperplasia, often resulting from chronic hypocalcemia in the setting of renal failure, and resolves when the hypocalcemia is corrected with renal transplant. However, transplant failure can result in recurrent HPT that may require parathyroid removal (*2*).

Parathyroid imaging is important for preoperative localization of hyperfunctioning parathyroid tissue. Originally advocated for patients who had undergone previous neck exploration and had persistent or recurrent HPT, preoperative parathyroid imaging has proven to be beneficial for initial identification of hyperfunctioning glands because it reduces operative time, costs, and failure rates. Past imaging techniques have involved ^{201}Tl- and ^{99m}Tc-pertechnetate and ^{99m}Tc-sestamibi with ^{123}I. Currently, a single-radionuclide, ^{99m}Tc-sestamibi (methoxyisobutylisonitrile [MIBI]) dual-phase protocol is accepted as the standard for localizing HPT because it has acceptable sensitivity and is cost-effective (*3–5*). Studies using this technique for initial preoperative detection of parathyroid adenomas have shown sensi-

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TABLE 1
Summary of Expected I/D and Right/Left Thyroid Ratios

Disease	I/D ratio
Benign	$\gg$1
Hyperplasia	>1 <Benign
Adenoma	>1 >Hyperplasia <Benign

tivity and specificity values ranging from 82% to 100% and from 89% to 100%, respectively. However, results for preoperative diagnosis of parathyroid hyperplasia have been poor, with sensitivities ranging from 37% to 80% (*6–8*). One group recently reported a sensitivity of 84% for detecting adenomas using a criterion whereby prolonged retention of radiotracer by 2 or more foci was interpreted as hyperplasia (*9*).

We believe dual-phase ^{99m}Tc-MIBI imaging is more sensitive than reported previously for parathyroid hyperplasia. Thus, we designed a study with 2 purposes. First, we sought to determine if dual-phase ^{99m}Tc-MIBI imaging is more sensitive for detecting HPT using a larger patient population. Additionally, we attempted to quantitate the data using a thyroid region of interest (ROI) as a road map on the immediate and delayed images. This helped to identify the ROI and differentiate between parathyroid hyperplasia, parathyroid adenoma, and normal parathyroid when the diagnosis was unclear from image interpretation alone. The immediate/delayed image ratio (I/D ratio) was expected to be different in normal parathyroid, hyperplasia, and adenoma. The expected values for the I/D ratio are summarized in Table 1.

MATERIALS AND METHODS

A retrospective analysis of 54 patients (34 female, 20 male) who underwent dual-phase ^{99m}Tc-MIBI imaging was performed. The average age of patients was 53.3 ± 15.6 y (range, 16–86 y). There were 8 (14.8%) with normal parathyroid, 21 (38.9%) with parathyroid hyperplasia (positive pathology or positive scan), and 25 (46.3%) with parathyroid adenoma (positive pathology).

Dual-Phase Parathyroid Imaging Protocol

Parathyroid images were acquired using a dual-phase imaging protocol with patients receiving 740 MBq (20 mCi) ^{99m}Tc-MIBI. Images were acquired at 20 min (immediate phase) and 2 h (delayed phase) after injection. Immediate-phase imaging consisted of a 5-min anterior pinhole image followed by a 5-min image of the upper thorax using a low-energy, high-resolution, parallel-hole collimator. The delayed image consisted of the same acquisitions as for the immediate phase plus additional 5-min right and left ante-

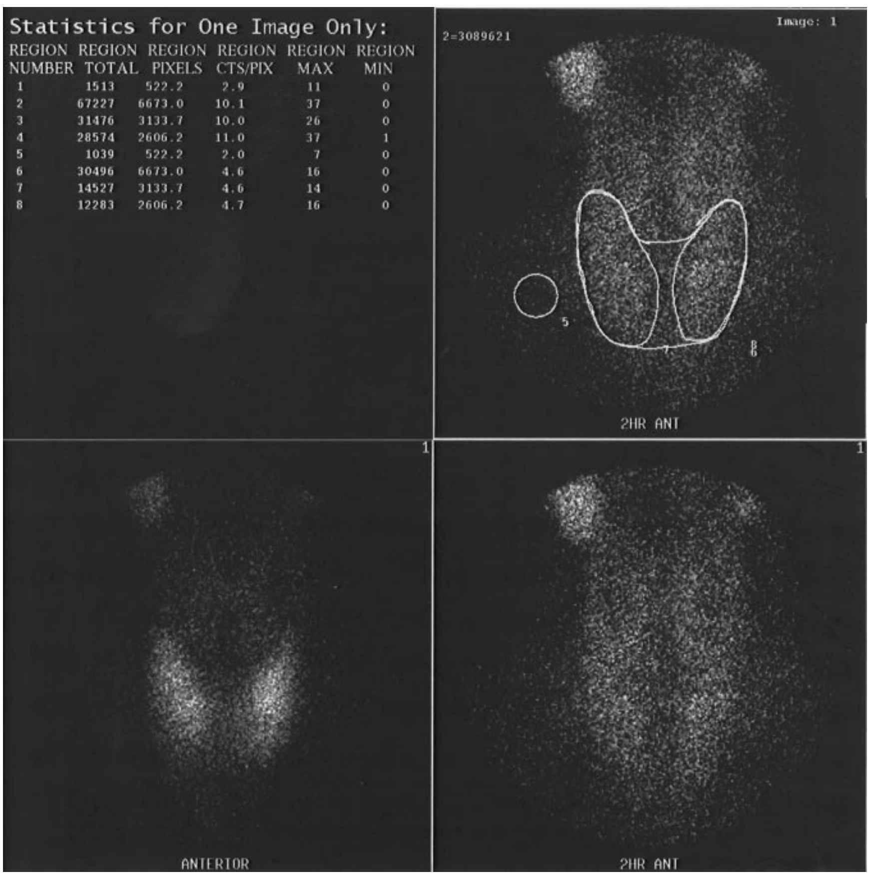

FIGURE 1. ROIs used for I/D ratio calculation.

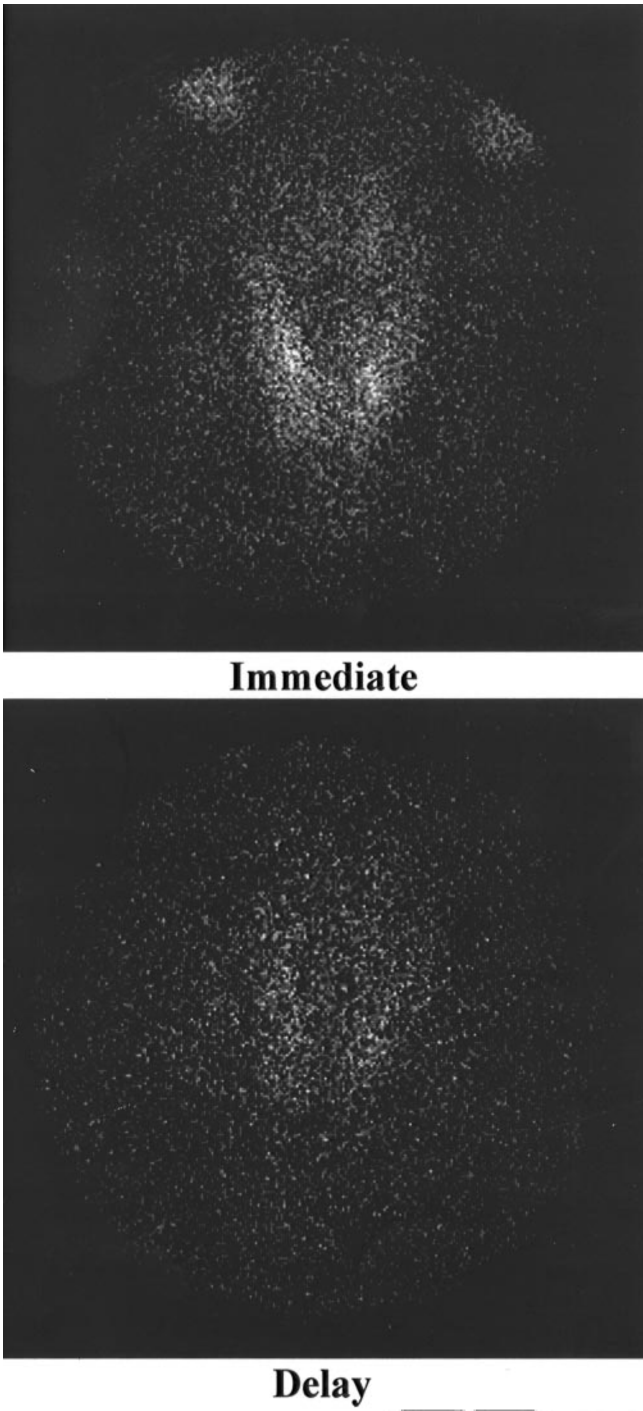

FIGURE 2. Dual-phase images from patient diagnosed with bilateral hyperplasia confirmed by histopathology after subtotal parathyroidectomy.

rior oblique pinhole images. All images were acquired using a 256 × 256 matrix on a dual-head gamma camera (Picker PRISM 2000; Marconi Medical Systems, Cleveland, OH).

Images of all patients were interpreted retrospectively by a board-certified nuclear medicine physician who was unaware of the clinical diagnosis and histopathology results when such results were known. Scans were interpreted for hyperfunctioning parathyroid tissue using the following criteria introduced by Klieger and O'Mara (*9*): Prolonged retention of radiotracer on the delayed images relative to thyroid activity appearing as a solitary focus was interpreted as an adenoma; 2 or more foci of persistent radiotracer activity on delayed images was interpreted as hyperplasia; no radiotracer retention on delayed images relative to thyroid activity was considered a normal scan.

Bilateral neck exploration and parathyroidectomy was performed on 46 of 54 patients. Resected parathyroid tissue

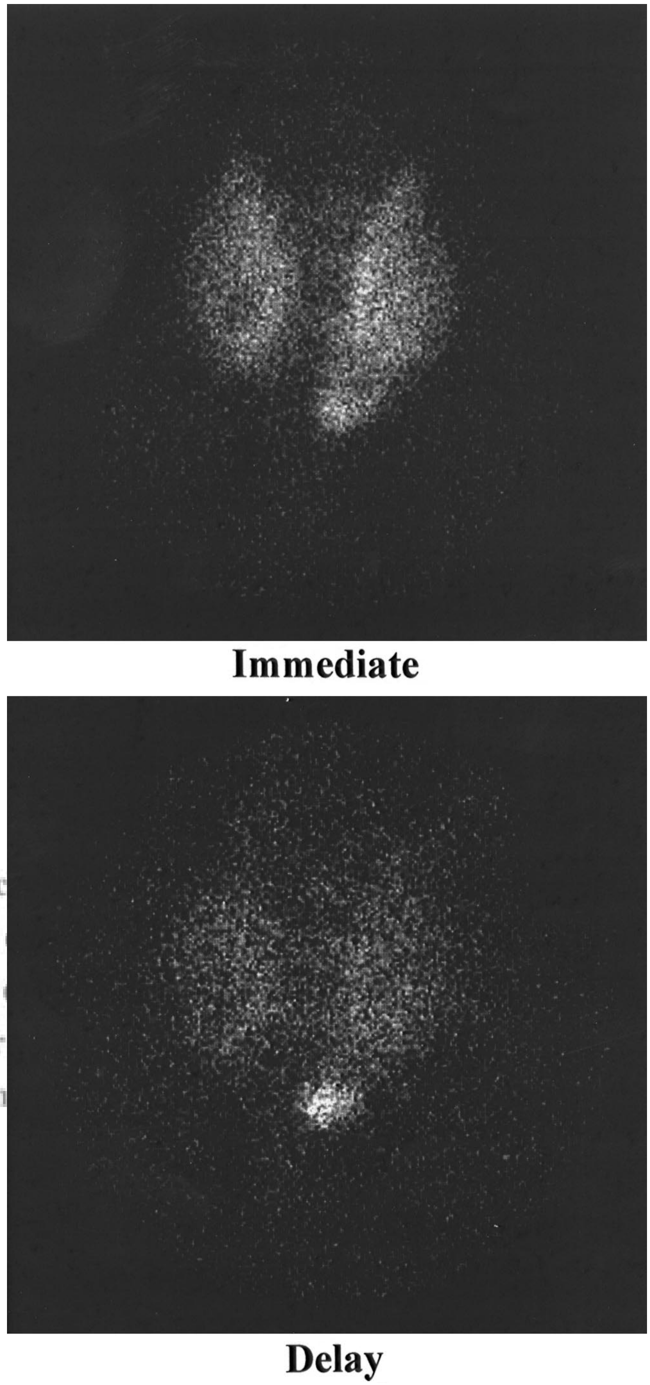

FIGURE 3. Dual-phase images from patient with nuclear medicine diagnosis of left inferior adenoma that was confirmed by pathology after left inferior excision.

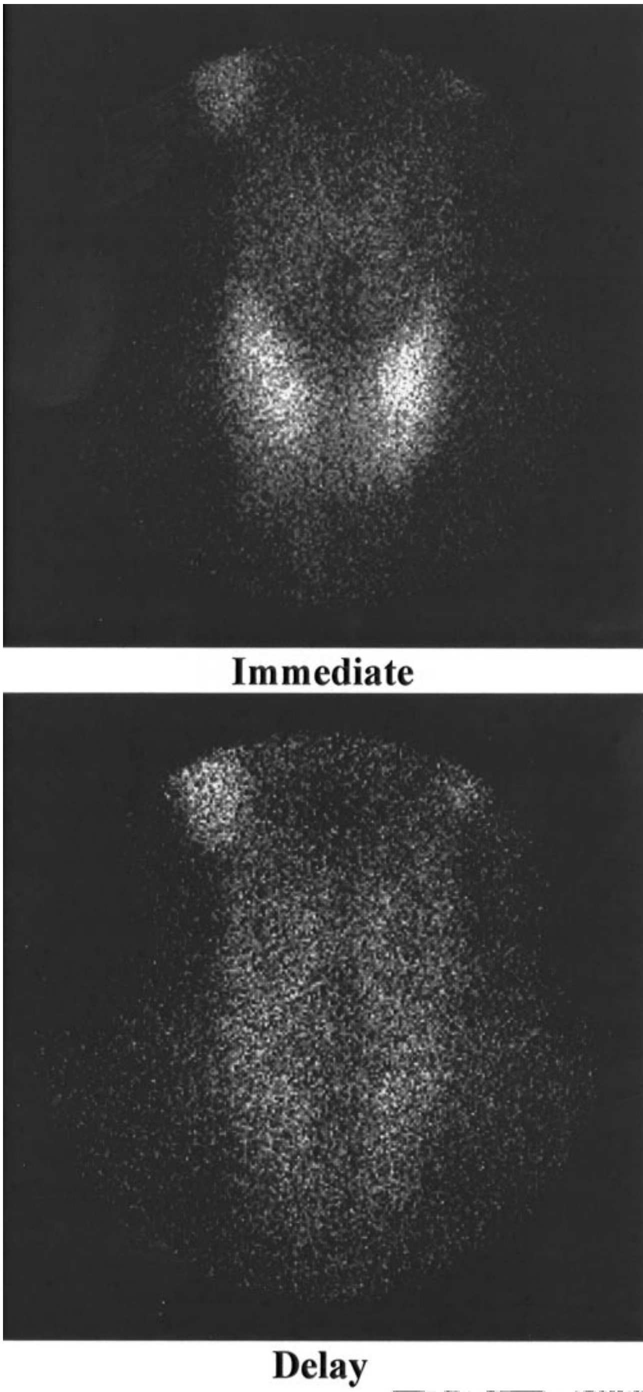

FIGURE 4. Typical benign dual-phase ^{99m}Tc-MIBI parathyroid images.

specimens were submitted for pathologic examination to obtain a definitive diagnosis. A scan was considered true-positive if it showed a solitary focus of activity on delayed imaging corresponding to the location of the adenomatous tissue resected and found to be parathyroid adenoma on histopathology or a scan was positive if it showed multiple foci of activity on delayed imaging corresponding to the locations of hyperplastic tissue resected and found to be hypercellular parathyroid on histopathology. Scans were also true-negative if no activity focus was seen or, if para-

TABLE 2
Average I/D Ratios for Thyroid, Left and Right Lobe Regions Grouped for Benign, Hyperplasia, and Adenoma Groups

Thyroid	I/D ratio
Benign	3.10 ± 0.77
Hyperplasia	2.26 ± 0.68
Adenoma	2.80 ± 0.95

Results are expressed as average ± 1 SD.

thyroidectomy was performed anyway, and the specimens were found to be normal by histopathology.

Thyroid ROI Analysis and I/D Ratio Calculation

I/D ratios were calculated using the immediate and delayed anterior pinhole images. Images were analyzed by a certified medical physicist using the Picker Odyssey (Marconi Medical Systems) workstation platform. ROIs were drawn over the thyroid on the immediate and delayed images (Fig. 1). The counts per pixel were calculated and then background subtraction was performed for each region. An I/D ratio was calculated by dividing the background-subtracted immediate thyroid region counts per pixel by the background-subtracted delayed thyroid region counts per pixel. Mean I/D ratios were then calculated for the thyroid region for each pathology type. The results were analyzed using a 2-tailed Student *t* test to determine the significance of the differences in the mean ratios between normal parathyroid and hyperplasia, normal parathyroid and adenoma, and hyperplasia and adenoma.

RESULTS

The sensitivity and specificity of dual-phase ^{99m}Tc MIBI parathyroid scans was found to be 82% and 96% for parathyroid adenoma and 91% and 88% for parathyroid hyperplasia, respectively, in 46 of 54 patients who underwent parathyroid resection. Figures 2–4 show examples of true-positive scans for parathyroid adenoma, hyperplasia, and benign parathyroid from the study patient population.

Figure 1 shows the ROIs used for calculation of the I/D ratio. The mean I/D thyroid ratio for normal patients was 3.10 ± 0.77 (range, 2.40–4.71). As predicted, the mean I/D thyroid ratio for the parathyroid hyperplasia cases was lower (2.26 ± 0.68; range, 0.78–3.73) than the normal ratio. For adenoma cases, the mean I/D thyroid ratio was 2.80 ±

TABLE 3
Results of 2-Tailed Student *t* Test Performed on I/D Thyroid Ratios

I/D ratio	*P*
Benign vs. hyperplasia	0.020
Benign vs. adenoma	0.381
Hyperplasia vs. adenoma	0.033

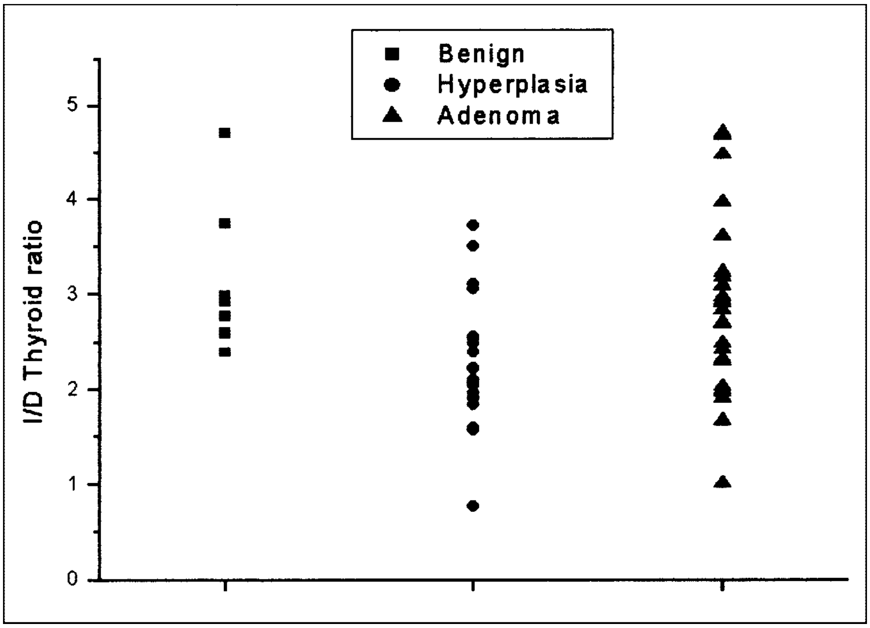

FIGURE 5. I/D thyroid ratios for benign parathyroid, hyperplasia, and adenoma.

0.95 (range, 1.07–4.72). Figure 5 shows a plot of the I/D ratio data and illustrates the range in the calculated ratios. Figure 6 shows a bar graph of the I/D ratio for the thyroid region. Error bars in Figure 6 represent ±1 SD. The average ratios from the thyroid region are summarized in Table 2 for the normal, hyperplasia, and adenoma groups. A 2-tailed Student *t* test was performed to evaluate whether the differences in the mean I/D ratios were statistically significant ($P < 0.05$ was considered to be statistically significant). The difference between the mean I/D ratio was found to be significant for normal parathyroid versus parathyroid hyperplasia ($P = 0.020$) and for parathyroid hyperplasia versus parathyroid adenoma ($P = 0.033$). The difference in the mean I/D ratios for normal parathyroid versus parathyroid adenoma cases was not significant ($P = 0.381$). Results of the Student *t* test are given in Table 3.

DISCUSSION

Our sensitivity and specificity for parathyroid hyperplasia equaled or exceeded these values in other studies (*6–9*). Even though our study was retrospective, it included the largest number of patients with proven parathyroid hyperplasia who underwent preoperative dual-phase ^{99m}Tc-MIBI imaging. Given our results for hyperplasia, we believe it is the noninvasive diagnostic imaging test of choice for localizing hyperfunctioning parathyroid tissue of any type before parathyroidectomy.

Our purpose was also to establish a quantitative method to help distinguish adenomas from hyperplasia when scan interpretation is uncertain. Although the differences between the mean I/D ratios were not as large as initially expected, we believe the differences in mean I/D ratios support using this

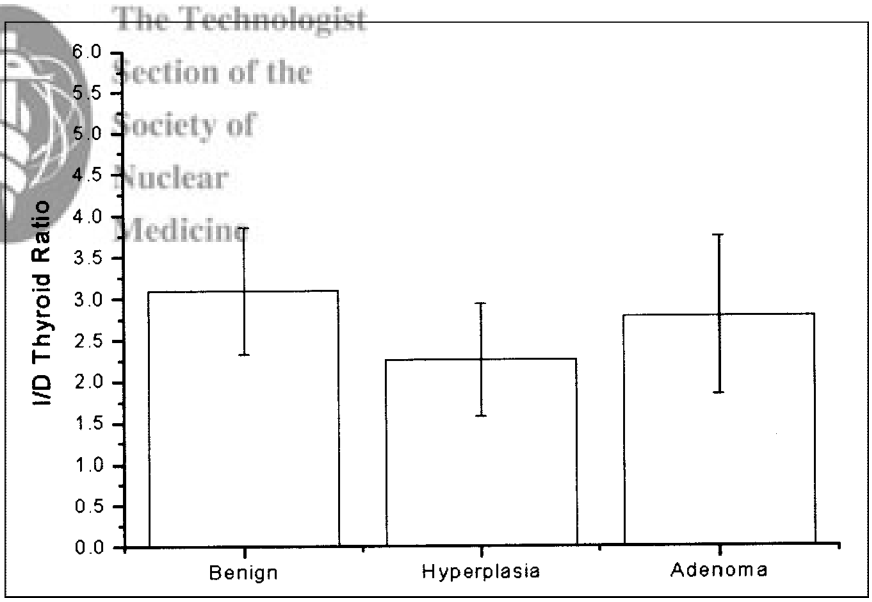

FIGURE 6. Average I/D ratios of thyroid region for benign parathyroid, hyperplasia, and adenoma.

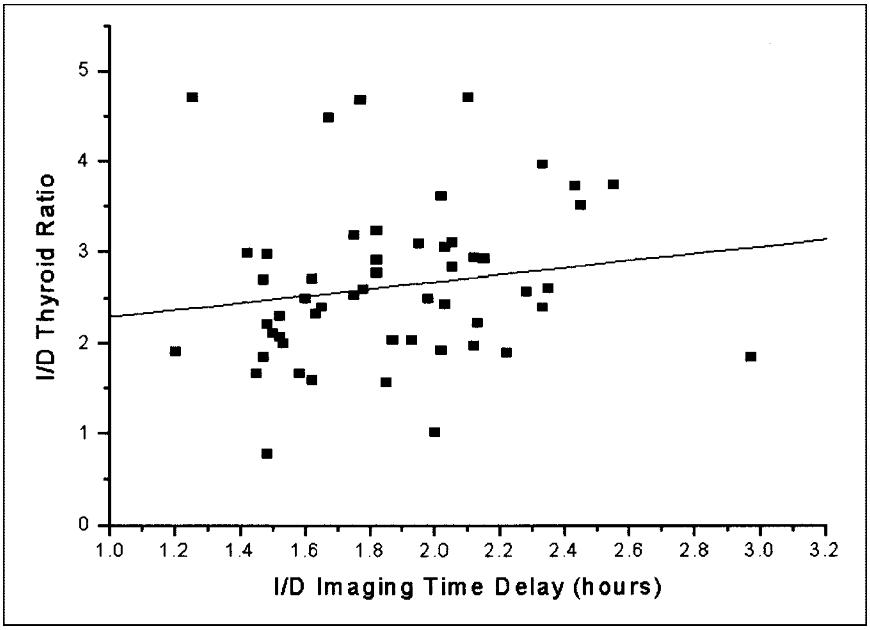

FIGURE 7. Plot of I/D imaging time interval vs. calculated I/D thyroid ratio. Line represents line of best fit having equation y = 0.3824x + 1.916 (r^2 = 0.0247).

quantitation method only in uncertain cases. There was considerable variation in the I/D ratios, and the overlap in the range made it difficult to determine a precise I/D ratio for each type of pathology. Many investigators have tried to quantitate parathyroid imaging data to improve diagnostic reliability, but our study shows that there are wide variations.

One of the potential sources of variation was the time interval between immediate and delayed image acquisitions because delayed images were not always acquired at 2 h, and some images were acquired as long as 3 h after injection. Because of the rapid thyroid clearance time for ^{99m}Tc-MIBI (27 ± 13 min) (*10*), it might be expected that altering the time between immediate and delayed images would affect the I/D ratio, but this is not true. A plot of the I/D ratio versus I/D acquisition interval time (Fig. 7) did not appear to be correlated well, although, there does appear to be a slight trend toward an increasing ratio as the delay time interval is increased.

CONCLUSION

Using more appropriate criteria for scan interpretation, dual-phase ^{99m}Tc-MIBI parathyroid imaging is more sensitive in diagnosing parathyroid hyperplasia than previously reported. Quantitation has limited value.

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